CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074242

Trade Name : NAPROXEN SODIUM TABLETS USP

Generic Name: Naproxen Sodium Tablets USP 275mg and 550mg

Sponsor : Sidmak Laboratories, Inc.

Approval Date: June 20, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074242

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Medical Review(s)				
Chemistry Review(s)	X			
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Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
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Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074242

APPROVAL LETTER

ANDA 74-242

JUN 20 1996

Sidmak Laboratories, Inc.
Attention: Arun D. Kulkarni
17 West Street
P.O. Box 371
East Hanover, NJ 07936

Dear Sir:

This is in reference to your abbreviated new drug application dated July 2, 1992, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Naproxen Sodium Tablets USP, 275 mg and 550 mg.

Reference is also made to your amendments dated August 30, 1993, June 13, 1994, May 16, 1996, and June 17, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Naproxen Sodium Tablets USP, 275 mg (250 mg base) and 550 mg (500 mg base) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Anaprox®, 250 mg base, and Anaprox DS®, 500 mg base, of Syntex (FP) Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 6/20/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-242
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-8/P.Savino
HFD-610/J.Phillips

Endorsements:
HFD-623/J.Clark/5-30-96
HFD-623/V.Sayeed, Ph.D.
HFD-617/J.Wilson/CSO/6-
HFD-613/C.Park/6-11-96
HFD-613/A.Vezza/6-12-96
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F/T by: bc/6-13-96

/S/ 3/96

/S/ 6/20/96

APPROVAL

/S/ 6/19/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074242

FINAL PRINTED LABELING

NDC 50111-559-03

Naproxen Sodium Tablets, USP

550 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Sidmak® LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen Sodium, USP..... 550 mg

Dispense in a well-closed container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert.

N 3 50111-559-03 5

20 [illegible]

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

Control No.:
Exp. Date:
Iss. 9/95

NDC 50111-559-02

Naproxen Sodium Tablets, USP

550 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Sidmak LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen Sodium, USP..... 550 mg

Dispense in a well-closed container as defined in the USP.

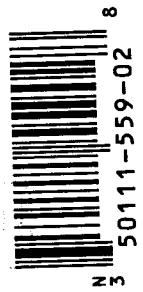
Store at controlled room temperature 15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert.

Control No.:
Exp. Date:

Rev. 9/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936



NDC 50111-559-01

Naproxen Sodium Tablets, USP

550 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Sidmak. LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen Sodium, USP ..... 550 mg
Dispense in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Control No.
Exp. Date:
Rev. 9/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

NDC 50111-558-03

Naproxen Sodium Tablets, USP

275 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Sidmak® LABORATORIES, INC.

JUN 2 C 995

EACH TABLET CONTAINS:
Naproxen Sodium, USP..... 275 mg

Dispense in a well-closed container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert.

N 3 50111-558-03 8

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

Control No.:
Exp. Date:
Iss. 9/95

NDC 50111-558-02

Naproxen Sodium Tablets, USP

275 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Sidmak LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen Sodium, USP..... 275 mg

Dispense in a well-closed container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert.

Control No.:
Exp. Date:

Rev. 9/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

3 50111-558-02 1

NDC 50111-558-01

Naproxen Sodium Tablets, USP

275 mg

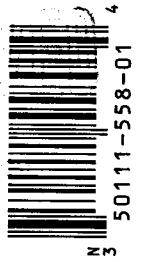
CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Sidmak. LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen Sodium, USP ..... 275 mg
Dispense in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Control No.:
Exp. Date:
Rev. 9/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936



NDC 50111-558-01

Naproxen Sodium Tablets, USP

275 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Sidmak. LABORATORIES, INC.

EACH TABLET CONTAINS:
Naproxen Sodium, USP ..... 275 mg
Dispense in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Control No.:
Exp. Date:
Rev. 9/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 2 years have not been established. Pediatric dosing recommendations for juvenile arthritis are based on well-controlled studies. There are no adequate effectiveness or dose-response data for other pediatric conditions, but the experience in juvenile arthritis and other use experience have established that single doses of 2.5 to 5 mg/kg (as naproxen oral suspension, see **DOSAGE AND ADMINISTRATION** section), with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age.

ADVERSE REACTIONS: The following adverse reactions are divided into three parts based on frequency and whether or not the possibility exists of a causal relationship between naproxen and these adverse events. In those reactions listed as "Probable Causal Relationship" there is at least one case for each adverse reaction where there is evidence to suggest that there is a causal relationship between drug usage and the reported event.

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen daily (see **CLINICAL PHARMACOLOGY**).

In controlled clinical trials with about 80 children and in well monitored open-label studies with about 400 children with juvenile arthritis, treated with naproxen, the incidence of rash and prolonged bleeding times were increased, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in children than in adults.

The following adverse reactions are divided into three parts based on frequency and causal relationship.

Incidence Greater Than 1% (Probable Causal Relationship)

Gastrointestinal: constipation*, heartburn*, abdominal pain*, nausea*, dyspepsia, diarrhea, and stomatitis.
Central Nervous System: headache*, dizziness *, drowsiness*, lightheadedness, and vertigo.
Dermatologic: itching (pruritus)*, skin eruptions*, ecchymoses*, sweating, purpura.
Special Senses: tinnitus*, hearing disturbances, visual disturbances.
Cardiovascular: edema*, dyspnea*, palpitations.
General: thirst.

*Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

Incidence Less Than 1% (Probable Causal Relationship)

The following adverse reactions were reported less frequently than 1% during controlled clinical trials and through voluntary reports since marketing. Those reactions observed through voluntary reporting since marketing are italicized.

Gastrointestinal: *Abnormal liver function tests, colitis,* gastrointestinal bleeding *and/or perforation, hematemesis,* jaundice, pancreatitis, melena, vomiting.
Renal: *Glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis.*
Hematologic: Agranulocytosis, *eosinophilia, granulocytopenia, leukopenia,* thrombocytopenia.
Central Nervous System: *Depression, dream abnormalities,* inability to concentrate, *insomnia, malaise, myalgia and muscle weakness.*
Dermatologic: *Alopecia, photosensitive dermatitis,* urticaria, skin rashes, *photosensitivity reactions resembling porphyria cutanea tarda and epidermolysis bullosa.*
Special Senses: *Hearing impairment.*
Cardiovascular: *Congestive heart failure.*
Respiratory: *Eosinophilic pneumonitis.*
General: *Anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills a fever).*

Incidence Less Than 1% (Causal Relationship Unknown)

These observations are being listed to serve as alerting information to the physician.
Hematologic: *Aplastic anemia, hemolytic anemia.*
Central Nervous System: *Aseptic meningitis, cognitive dysfunction.*
Dermatologic: *Epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome.*
Gastrointestinal: *Non-peptic gastrointestinal ulceration, ulcerative stomatitis.*
Cardiovascular: *Vasculitis.*
General: *Hypoglycemia, hypoglycemia.*

OVERDOSAGE: Significant naproxen overdosage may be characterized by drowsiness, heartburn, indigestion, nausea or vomiting. Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced seizures, but it is not clear whether or not these were drug related. It is not known what dose of the drug would be life threatening. The oral LD_{50} of naproxen is 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters and greater than 1000 mg/kg in dogs.

Should a patient ingest a large number of tablets, accidentally or purposefully, the stomach may be emptied and usual supportive measures employed. In animals 0.5 g/kg of activated charcoal was effective in reducing plasma levels of naproxen. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding.

DOSAGE AND ADMINISTRATION:

Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis: The recommended dose of naproxen sodium is 275 mg (equivalent to 250 mg naproxen with 25 mg sodium) or 550 mg (equivalent to 500 mg of naproxen with 50 mg sodium) twice daily. During long-term administration, the dose may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. The morning and evening doses do not have to be equal in size and the administration of the drug more frequently than twice daily is not necessary.

In patients who tolerate lower doses well, the dose may be increased to naproxen sodium 1650 mg per day for limited periods when a higher level of anti-inflammatory/analgesic activity is required. When treating such patients with naproxen sodium 1650 mg/day, the physician should observe sufficient increased clinical benefits to offset the potential increased risk (see **CLINICAL PHARMACOLOGY: Individualization of Dosage**).

Juvenile Arthritis: The recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses (i.e., 5 mg/kg given twice a day). Naproxen sodium tablets are not well suited to this dosage so use of naproxen oral suspension is recommended for this indication.

Management of Pain, Primary Dysmenorrhea and Acute Tendinitis and Bursitis: The recommended starting dose is 550 mg of naproxen sodium, followed by 550 mg every 12 hours or 275 mg every 6 to 8 hours as required. The initial total daily dose should not exceed 1375 mg of naproxen sodium. Thereafter, the total daily dose should not exceed 1100 mg of naproxen sodium. (see **CLINICAL PHARMACOLOGY** and **Individualization of Dosage**).

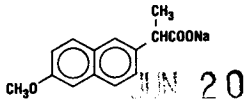
Acute Gout: The recommended starting dose is 825 mg of naproxen sodium, followed by 275 mg every 8 hours until the attack has subsided.

HOW SUPPLIED: Naproxen Sodium Tablets, USP:
275 mg - Light blue, oval, unscored, film coated tablets in bottles of 100, 500 and 1000.
Imprinted: SL 558
550 mg - Blue, oval, unscored, film coated tablets in bottles of 100, 500 and 1000.
Imprinted: SL 559
Store at controlled room temperature 15° - 30°C (59° - 86°F).
Dispense in a well-closed container as defined in the USP.
CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

P08-0558 Iss. 2/96

DESCRIPTION: Naproxen sodium is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs. The chemical name for naproxen sodium is (-)-Sodium 6-methoxy-α-methyl-2-naphthaleneacetate. It has the following structural formula:



MW = 252.25 Molecular Formula: $C_{14}H_{13}NaO_3$

Naproxen sodium is a white to creamy, crystalline solid, freely soluble in water at neutral pH.

Each tablet, for oral administration, contains 275 mg or 550 mg naproxen sodium, equivalent to 250 mg or 500 mg naproxen with 25 mg (about 1 mEq) or 50 mg (about 2 mEq) of sodium, respectively. In addition, each tablet contains the following inactive ingredients: carnauba wax, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, talc, titanium dioxide, D&C Yellow #10 (275 mg and 550 mg), FD&C Blue #1 (275 mg and 550 mg) and FD&C Blue #2 (550 mg only).

P08-0558

NAPROXEN SODIUM TABLETS, USP

Iss.2/96

CLINICAL PHARMACOLOGY: Naproxen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. The sodium salt of naproxen, has been developed as a more rapidly absorbed formulation of naproxen for use as an analgesic. The naproxen anion inhibits prostaglandin synthesis but beyond this its mode of action is unknown.

Pharmacokinetics: Naproxen itself is rapidly and completely absorbed from the gastrointestinal tract with an *in vivo* bioavailability of 95%. The elimination half-life of naproxen ranges from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days and the degree of naproxen accumulation is consistent with this half-life.

Absorption: After oral administration of naproxen sodium tablets, peak plasma levels are attained in 1 to 2 hours.

Distribution: Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough C_{ss} 36.5, 49.2, and 56.4 mg/L with 500, 1000, and 1500 mg daily doses of naproxen). However, the concentration of unbound naproxen continues to increase proportionally to dose.

Metabolism: Naproxen is extensively metabolized to 6-0-desmethyl naproxen and both parent and metabolites do not induce metabolizing enzymes.

Elimination: The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%) 6-0-desmethyl naproxen (less than 1%), or their conjugates (66-92%). The plasma half-life of the naproxen anion in humans ranges from 12 – 17 hours. The corresponding half-lives of both naproxen's metabolites and conjugates are shorter than 12 hours and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. In patients with renal failure metabolites may accumulate.

Special Populations:

Children: In children of 5 to 16 years of age with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen suspension (see **DOSAGE AND ADMINISTRATION**) were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in children and adults. Pharmacokinetic studies of naproxen were not performed in children of less than 5 years of age.

Renal Insufficiency: Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites, and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency.

Clinical Studies: ***General Information:*** Naproxen has been studied in patients with rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendinitis and bursitis, and acute gout. Improvement in patients treated for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time. Generally, response to naproxen has not been found to be dependent on age, sex, severity or duration of rheumatoid arthritis.

In patients with osteoarthritis, the therapeutic action of naproxen has been shown by a reduction in joint pain or tenderness, an increase in range of motion in knee joints, increased mobility as demonstrated by a reduction in walking time, and improvement in capacity to perform activities of daily living impaired by the disease.

In a clinical trial comparing standard formulations of naproxen 375 mg BID (750 mg a day) versus 750 mg BID (1500 mg a day), 9 patients in the 750 mg group terminated prematurely because of adverse events. Nineteen patients in the 1500 mg group terminated prematurely because of adverse events. Most of these adverse events were gastrointestinal events.

In clinical studies in patients with rheumatoid arthritis, osteoarthritis, and juvenile arthritis, naproxen has been shown to be comparable to aspirin and indomethacin in controlling the aforementioned measures of disease activity, but the frequency and severity of the milder gastrointestinal adverse effects (nausea, dyspepsia, heartburn) and nervous system adverse effects (tinnitus, dizziness, lightheadedness) were less in naproxen treated patients than in those treated with aspirin or indomethacin.

In patients with ankylosing spondylitis, naproxen has been shown to decrease night pain, morning stiffness and pain at rest. In double-blind studies the drug was shown to be as effective as aspirin, but with fewer side effects.

In patients with acute gout, a favorable response to naproxen was shown by significant clearing of inflammatory changes (e.g., decrease in swelling, heat) within 24 to 48 hours, as well as by relief of pain and tenderness.

Naproxen has been studied in patients with mild to moderate pain secondary to post-operative, orthopedic, post-partum episiotomy, and uterine contraction pain and dysmenorrhea. Onset of pain relief can begin within 30 minutes in patients taking naproxen sodium. Analgesic effect was shown by such measures as reduction of pain intensity scores, increase in pain relief scores, decrease in numbers of patients requiring additional analgesic medication, and delay in time to remedication. The analgesic effect has been found to last for up to 12 hours.

Naproxen may be used safely in combination with gold salts and/or corticosteroids; however, in controlled clinical trials, when added to the regimen of patients receiving corticosteroids it did not appear to cause greater improvement over that seen with corticosteroids alone. Whether naproxen has a "steroid-sparing" effect has not been adequately studied. When added to the regimen of

patients receiving gold salts, naproxen did result in greater improvement. Its use in combination with salicylates is not recommended because there is evidence that aspirin increases the rate of excretion of naproxen and data are inadequate to demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, as with other NSAIDS the combination may result in higher frequency of adverse events than demonstrated for either product alone.

In ^{51}Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1100 mg of naproxen sodium has been demonstrated to cause statistically significantly less gastric bleeding and erosion than 3250 mg of aspirin.

Individualization of Dosage: Onset of pain relief can begin within 30 minutes in patients taking naproxen sodium.

The recommended strategy for initiating therapy is to choose a formulation and a starting dose likely to be effective for the patient and then adjust the dosage based on observation of benefit and/or adverse events. A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients (see **PRECAUTIONS**).

Analgesia/Dysmenorrhea/Bursitis and Tendinitis: Because the sodium salt of naproxen is more rapidly absorbed, naproxen sodium is recommended for the management of acute painful conditions when prompt onset of pain relief is desired. The recommended starting dose is 550 mg followed by 550 mg every 12 hours or 275 mg every 6 to 8 hours, as required. The initial total daily dose should not exceed 1375 mg of naproxen sodium. Thereafter, the total daily dose should not exceed 1100 mg of naproxen sodium.

Acute Gout: The recommended starting dose is 825 mg of naproxen sodium followed by 275 mg every 8 hours as needed.

Osteoarthritis/Rheumatoid Arthritis/Ankylosing Spondylitis: The recommended dose of naproxen sodium is 275 mg or 550 mg taken twice daily (morning and evening). During long-term administration the dose of naproxen sodium may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. In patients who tolerate lower doses well, the dose may be increased to 1650 mg per day when a higher level of anti-inflammatory/analgesic activity is required. When treating patients with naproxen sodium 1650 mg/day, the physician should observe sufficient increased clinical benefit to offset the potential increased risk. The morning and evening doses do not have to be equal in size and administration of the drug more frequently than twice daily does not generally make a difference in response (see **CLINICAL PHARMACOLOGY**).

Juvenile Arthritis: The use of naproxen oral suspension allows for more flexible dose titration. In children, doses of 5 mg/kg/day produced plasma levels of naproxen similar to those seen in adults taking 500 mg of naproxen (see **CLINICAL PHARMACOLOGY**).

The recommended total daily dose is approximately 10 mg/kg given in 2 divided doses (i.e., 5 mg/kg given twice a day). (See **DOSAGE AND ADMINISTRATION**).

INDICATIONS AND USAGE: Naproxen sodium tablets are indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and juvenile arthritis.

Naproxen sodium tablets are also indicated for the treatment of tendinitis, bursitis, acute gout, and for the management of pain and primary dysmenorrhea.

CONTRAINDICATIONS: Naproxen sodium is contraindicated in patients who have had allergic reactions to prescription as well as to over-the-counter products containing naproxen. It is also contraindicated in patients in whom aspirin or other nonsteroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis, and nasal polyps. Both types of reactions have the potential of being fatal. Anaphylactoid reactions to naproxen, whether of the true allergic type or the pharmacologic idiosyncratic (e.g., aspirin hypersensitivity syndrome) type, usually but not always occur in patients with a known history of such reactions. Therefore, careful questioning of patients for such things as asthma, nasal polyps, urticaria, and hypotension associated with nonsteroidal anti-inflammatory drugs before starting therapy is important. In addition, if such symptoms occur during therapy, treatment should be discontinued.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy: Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date with naproxen sodium have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS:

General: NAPROXEN SODIUM SHOULD NOT BE USED CONCOMITANTLY WITH OTHER NAPROXEN PRODUCTS SINCE THEY ALL CIRCULATE IN THE PLASMA AS THE NAPROXEN ANION.

If the steroid dose is reduced or eliminated during therapy, the steroid dosage should be reduced slowly and the patients should be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Patients with initial hemoglobin values of 10 grams or less who are to receive long-term therapy should have hemoglobin values determined periodically.

The antipyretic and anti-inflammatory activities of the drug may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed non-infectious, non-inflammatory painful conditions.

Because of adverse eye findings in animal studies with drugs of this class it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of naproxen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome associated with naproxen containing products and other NSAIDS since they have been marketed.

A second form of renal toxicity has been seen in patients taking naproxen as well as other nonsteroidal anti-inflammatory drugs. In patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is typically followed by recovery to the pretreatment state.

Naproxen and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with caution in patients with significantly impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. Caution should be used if the drug is given to patients with creatinine clearance of less than 20 mL/minute because accumulation of naproxen metabolites has been seen in such patients.

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose.

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Hepatic Function: As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with naproxen sodium. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with naproxen as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), naproxen sodium should be discontinued.

Fluid Retention and Edema: Peripheral edema has been observed in some patients receiving naproxen. Since each naproxen sodium tablet contains approximately 25 mg or 50 mg of sodium (about 1 mEq per each 275 mg naproxen sodium tablet), this should be considered in patients whose overall intake of sodium must be severely restricted. For these reasons, naproxen sodium should be used with caution in patients with fluid retention, hypertension or heart failure.

Information for Patients: Naproxen sodium, like other drugs of its class, is not free of side effects. The side effects of naproxen sodium can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) are often essential agents in the management of arthritis and have a major role in the treatment of pain, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see **WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS** sections) and likely benefits of naproxen treatment, particularly when it is used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during therapy with naproxen sodium.

Laboratory Tests: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow patients chronically treated with naproxen for signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up and what they should do if certain signs and symptoms do appear (see **WARNINGS - Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy**).

Drug Interactions: The use of NSAIDs in patients who are receiving ACE inhibitors may potentiate renal disease states (see **PRECAUTIONS, *Renal Effects***).

In vitro studies have shown that naproxen anion, because of its affinity for protein, may displace from their binding sites other drugs which are also albumin-bound (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Theoretically, the naproxen anion itself could likewise be displaced. Short-term controlled studies failed to show that taking the drug significantly affects prothrombin times when administered to individuals on coumarin-type anticoagulants. Caution is advised nonetheless, since interactions have been seen with other nonsteroidal agents of this class. Similarly, patients receiving the drug and a hydantoin, sulfonamide or sulfonylurea should be observed for signs of toxicity to these drugs (see **CLINICAL PHARMACOLOGY, Clinical Studies: *General Information***).

Concomitant administration of naproxen and aspirin is not recommended because naproxen is displaced from its binding sites during the concomitant administration of aspirin, resulting in lower plasma concentrations and peak plasma levels.

The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported. Naproxen sodium and other nonsteroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

Caution should be used if naproxen sodium is administered concomitantly with methotrexate. Naproxen sodium and other nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly increasing the toxicity of methotrexate.

Drug/Laboratory Test Interactions: Naproxen sodium may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of naproxen sodium may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-nitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen sodium be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen sodium may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

Carcinogenesis: A two-year study was performed in rats to evaluate the carcinogenic potential of naproxen at doses of 8, 16, and 24 mg/kg/day (50, 100, and 150 mg/m^2). The maximum dose used was 0.28 times the systemic exposure to humans at the recommended dose. No evidence of tumorigenicity was found.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B. Reproduction studies have been performed in rats at 20 mg/kg/day (125 mg/m^2/day, 0.23 times the human systemic exposure), rabbits at 20 mg/kg/day (220 mg/m^2/day, 0.27 times the human systemic exposure), and mice at 170 mg/kg/day (510 mg/m^2/day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due to the drug. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naproxen sodium should not be used during pregnancy unless clearly needed.

Non-teratogenic Effects: There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus, and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction, and abnormal prostaglandin E levels in preterm infants. Because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of the ductus arteriosus), use during third trimester should be avoided.

Nursing Mothers: The naproxen anion has been found in the milk of lactating women at a concentration of approximately 1% of that found in the plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

P08-0558

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074242

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3 2. ANDA # 74-242

3. NAME AND ADDRESS OF APPLICANT
Sidmak Laboratories, Inc.
Attention: Satish P. Patel, Ph.D.
17 West Street
East Hanover, NJ 07936

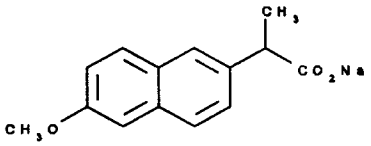
4. BASIS OF SUBMISSION Anaprox Tablets® ; Syntex
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME none
7. NONPROPRIETARY NAME Naproxen Sodium Tablets USP
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

July 2, 1992	Date of Application.
September 17, 1992	Unacceptable EER response.
November 18, 1992	CMC NA letter.
August 30, 1993	Packaging site amendment.
March 17, 1994	Bio NA letter.
June 13, 1994	Bio amendment.
September 8, 1994	Bio acceptable, L.Lesko.
May 3, 1995	CMC amendment; this review.
August 10, 1995	Second label review; revision needed.
December 15, 1995	CMC/label NA letter.
May 16, 1995	CMC/label amendment, this review.

10. PHARMACOLOGICAL CATEGORY NSAID
11. Rx or OTC Rx 12. RELATED IND/NDA/DMF(s) See sec. 37
13. DOSAGE FORMoral tablet 14. POTENCY 250mg, 375mg, 500mg.

15. CHEMICAL NAME AND STRUCTURE
Naproxen Sodium USP
$C_{14}H_{13}NaO_3$; M.W. = 252.24
(-)-Sodium 6-methoxy-α-methyl-2-naphthaleneacetate.
CAS [26159-34-2]



16. RECORDS AND REPORTS N/A

17. COMMENTS
The previous deficiencies are adequately addressed.

18. CONCLUSIONS AND RECOMMENDATIONS Approve
pending labeling

19. REVIEWER: Jon E. Clark DATE COMPLETED: May 30, 1996

cc: ANDA 74-242
DUP Jacket
Division File

Endorsements:
HFD-623/J.Clark /S/ 6/11/96
HFD-623/V.Sayee
X: NEW FIRMSNZ SIDMAK LTRS&REV 74242AP3.R
F/T by

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074242

BIOEQUIVALENCE REVIEW(S)

Naproxen, 275 mg and 500 mg, tablets
ANDA 74-242

Sidmak Laboratories, Inc.
Attention: Satish P. Patel
17 West Street
Post Office Box 371
East Hanover, NJ 07936

Dear Dr. Patel:

Reference is made to the *in vivo* bioequivalence studies and the waiver request supported by dissolution data submitted on July 2, 1992.

The Office of Generic Drugs/Division of Bioequivalence has reviewed this material and we have found the studies to be incomplete for the following reasons:

1. The name of the internal standard used in the assay should be included in the final report.

2. The potency of Lot 91-025T was not supplied.

3. The zero time values with which to compare "comparison and stability" sample analyses for freeze thaw and other stability investigations was not supplied.

You are required to take an action described under 21 CFR 314.96 which will amend this submission.

All responses and correspondence with regard to this letter should indicate the date of this letter, and be addressed to the Office of Generic Drugs/Division of Bioequivalence, HFD-650.

A representative of the Division of Bioequivalence is available to clarify this letter and to assist you with any questions; you may contact Jason A. Gross, Pharm.D., Chief Consumer Safety Officer at (301) 594-0315.

Sincerely yours,

Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

MAR 9 1994

Naproxen
500 mg Tablet
275 mg Tablet
ANDA # 74-242
Reviewer: Andre Jackson
WP #74242SDW.792

Sidmak Labs
Hanover, N.J.
Submission Dated:
July 2, 1992

Review of Fasting and Post-Prandial 550 mg Bioequivalence Studies Dissolution Data and Waiver Request for 275 mg Tablet

Background

Naproxen is an orally administered nonsteroidal anti-inflammatory drug(NSAID), which also has analgesic and antipyretic properties. The naproxen ion inhibits prostaglandin synthesis, but its action otherwise is unknown. Labeled indications for naproxen are for the acute or long-term treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, relief of moderate pain and for the treatment of primary dysmenorrhea. The recommended dosage is 275 mg or 550 mg given twice daily.

Naproxen sodium is readily and completely absorbed after oral administration of 550 mg, reported time of maximum concentration values of 1-2 hr and are expected to approximate the peak levels of 80 ug/ml after naproxen. The half-life of naproxen in plasma ranges from 12 to 15 hours. Enterohepatic recycling has been reported to occur. The drug is eliminted primarily by renal pathways with about 50% excreted in the urine after 24 hours with the recovery increasing to 94% after 5 days following a single oral dose. Less than 10% of the excreted drug is unchanged naproxen.

Fasting Study

Objective:

The aim of this study is to compare the oral absorption of naproxen tablets manufactured by Sidmak Pharmaceuticals with a commercial lot of the reference product, Anaprox tablets manufactured by Syntex following a single 550 mg dose.

Methods:

The study was conducted by (b)4 - Confidential Business under the direction of (b)4 Samples were analyzed by Ph (b)4 - Confidential Business

I. Characterization of Study Group:

A. Inclusion criteria

1. All volunteers selected for this study were male volunteers between the ages of 18 and 45 years. Weight range of the volunteers was within 10% of normal body weight relative to height and frame size.

2. Each volunteer was given a general physical examination within 30 days of initiation of the study. Each examination included blood pressure, general observations, history, complete hemogram (hemoglobin, hematocrit, WBC, differential), urinalysis (including microscopic), biochemistry (blood urea nitrogen, serum bilirubin [total]), HIV antibody screen. Volunteers selected for the study had no clinically significant abnormal findings.

3. Normal electrocardiogram

B. Exclusion Criteria:

1. Volunteers with a history of alcohol or drug addiction during the past two years, gastrointestinal, renal, hepatic or cardiovascular disease, tuberculosis, epilepsy, asthma.

2. Any noted EKG abnormality

3. History of adverse reactions or allergy to aspirin naproxen sodium, or other NSAID's.

4. Participation in a previous clinical trial or the donation of one pint or more of blood within the past 90 days.

5. Use of any OTC medication on a regular basis.

6. Positive screen for drugs of abuse

7. Positive HBsAg or HIV screen.

8. Subjects that smoke

C. Informed Consent:

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

The study was done in 24, healthy males.

A. Subjects fasted 10 hours overnight until 4.0 hrs after their scheduled dosing times. Water was not allowed from 2 hours before until 2 hours after dosing but was allowed ad lib thereafter.

Standard meals were provided at 4 and approximately 10 hours after dosing.

B. The products employed in the study were:

1. Test: Sidmak Pharmaceutical 550 mg naproxen tablet, Lot # 91-025, Lot Size (b)4 - tablets.

2. Reference product: Syntex 550 mg Anaproxen tablet, Lot#53534, expiration date 1/94.

There was a 14 day washout between doses.

C. A 550 mg dose (1 x 550 mg) of each product (test and reference) was administered at time zero with 240 ml of water. The randomization scheme is presented in table 1.

Table 1. Random Assignment of 26 subjects

Sequence	SUBJECT
A,B	3,4,7,8,10,11,13,16,18,20,21,23,25
B,A	1,2,5,6,9,12,14,15,17,19,22,24,26

Treatment A: Naproxen Tablets, 550 mg (1 Tablet) Sidmak

Treatment B: Anaprox Tablet, 550 mg (1 Tablet) Syntex PHARMACEUTICALS, INC.

The formulation for the 550 mg tablet is given in table 2.

Table 2. COMPOSITION OF THE 550 MG NAPROXEN TABLET

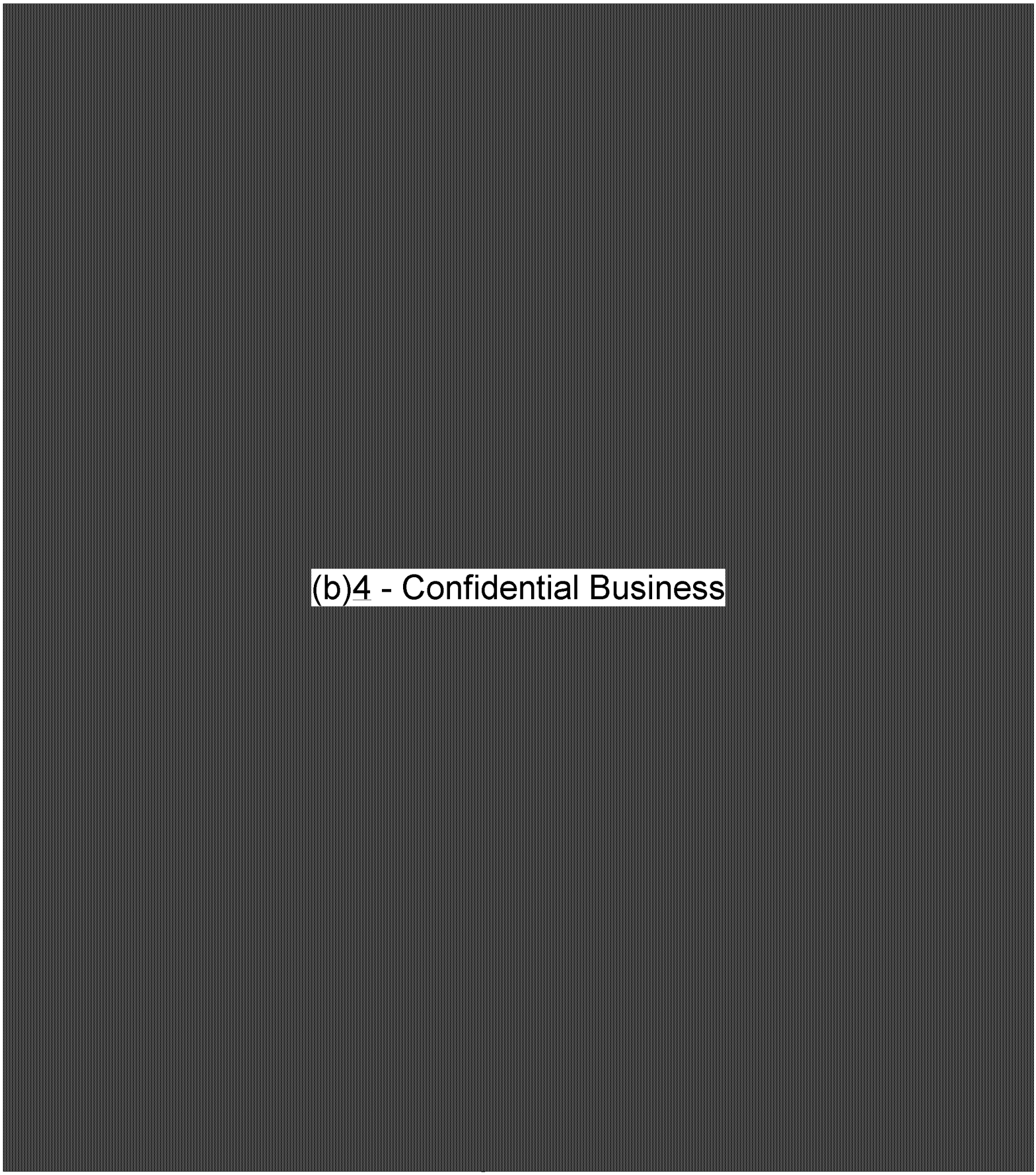
INGREDIENTS	MG/UNIT	%/UNIT
Naproxen sodium, (anhydrous) USP	550.0	69.42
Microcrystalline Cellulose, NF(avicel PH-102)	(b)4 - Confidential Business	
Povidone, USP		
*Purified water, USP		
Talc, USP #140		
Magnesium stearate, NF		
Opadry Blue,		
Opadry Clear,		
Purified water, USP		
Carnauba wax, NF powder		
Theoretical total weight of tablet in mg	792.3	100%

D. Plasma was collected pre-dose and at the following times post-dose: 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48 and 60 hours.

E. During the study subjects were monitored for adverse reactions.

III. Analytical

(b)4 - Confidential Business


(b)4 - Confidential Business